1: Immunity. 1995 Dec;3(6):673-82.

Identification and characterization of a new member of the TNF family that induces apoptosis.

Wiley SR, Schooley K, Smolak PJ, Din WS, Huang CP, Nicholl JK, Sutherland GR, Smith TD, Rauch C, Smith CA, et al.

Immunex Research and Development Corporation, Seattle, Washington 98101, USA.

A novel tumor necrosis factor (TNF) family member has been cloned and characterized. This protein, designated TNF-related apoptosis-inducing ligand (TRAIL), consists of 281 and 291 aa in the human and murine forms, respectively, which share 65% aa identity. TRAIL is a type II membrane protein, whose C-terminal extracellular domain shows clear homology to other TNF family members. TRAIL transcripts are detected in a variety of human tissues, most predominantly in spleen, lung, and prostate. The TRAIL gene is located on chromosome 3 at position 3q26, which is not close to any other known TNF ligand family members. Both full-length cell surface expressed TRAIL and picomolar concentrations of soluble TRAIL rapidly induce apoptosis in a wide variety of transformed cell lines of diverse origin.

PMID: 8777713 [PubMed - indexed for MEDLINE]

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L1     2599803 ANTIBOD?

=> s l1 and "apoptosis inducing molecule"
L2           44 L1 AND "APOPTOSIS INDUCING MOLECULE"

=> s l2 and TRAIL
L3            8 L2 AND TRAIL

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L4             4 DUP REMOVE L3 (4 DUPLICATES REMOVED)

=> d l4 1-4 cbib abs

L4   ANSWER 1 OF 4  CAPLUS  COPYRIGHT 2004 ACS on STN
2004:78443   Document No. 140:105276  Immune modulation with death
     receptor-induced apoptosis.  Shirwan, Haval (USA).  U.S. Pat. Appl. Publ.
     US 2004018170 A1 20040129, 19 pp.  (English).  CODEN: USXXCO.
     APPLICATION: US 2002-202613 20020723.
AB   The invention provides chimeric proteins comprising an apoptosis
     -inducing mol. fused to a member of a binding pair
     that is capable of binding to a selected cell that expresses a death
     receptor.  When the selected cell is exposed in vivo or ex vivo to the
     chimeric protein, the selected cell undergoes apoptosis.  The preferred
     embodiment is FasL protein fused to streptavidin.  The methods of using
     the chimeric proteins are especially beneficial in causing activated
lymphocytes
     to undergo apoptosis, thus modulating the immune response.  Patients with
     conditions such as asthma or allergy, or patients undergoing
     transplantation with allogeneic or xenogeneic tissue are examples of
     patients who benefit from the methods of this invention.

L4   ANSWER 2 OF 4  CAPLUS  COPYRIGHT 2004 ACS on STN
2003:829362   Document No. 139:336931  Antibodies specific to human
     apoptosis inducing molecule II for screening
     AIM II agonist/antagonist and for diagnosis and therapy of
     lymphadenopathy, autoimmune and immune disease, bone disease and neoplasm.
     Ebner, Reinhard; Yu, Guo-liang; Ruben, Steven M.; Ullrich, Stephen; Zhai,
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Yifan (Human Genome Sciences, Inc., USA). U.S. US 6635743 B1 20031021, 163 pp., Cont.-in-part of U.S. Ser. No. 252,656. (English). CODEN: USXXAM. APPLICATION: US 2000-523323 20000310. PRIORITY: US 1996-PV13923 19960322; US 1996-PV30157 19961031; US 1997-822953 19970321; US 1998-3886 19980107; US 1998-27287 19980220; US 1998-PV75409 19980220; US 1999-252656 19990219; US 1999-PV124041 19990311; US 1999-PV137457 19990604; US 1999-PV142657 19990706; US 1999-PV148326 19990811; US 1999-PV168380 19991202.

AB The present invention relates to a novel member of the TNF-Ligand superfamily. More specifically, isolated nucleic acid mols. are provided encoding a human **Apoptosis Inducing Mol.** II (AIM II). AIM II polypeptides are also provided, as are vectors, host cells and recombinant methods for producing the same. The invention further relates to screening methods for identifying agonists and antagonists of AIM II activity. Also provided are therapeutic methods for treating lymphadenopathy, aberrant bone development, autoimmune and other immune system diseases, graft vs. host disease, rheumatoid arthritis, osteoarthritis and to inhibit neoplasia, such as tumor cell growth.

L4 ANSWER 3 OF 4 CAPLUS COPYRIGHT 2004 ACS on STN

2001:545427 Document No. 135:136428 Immune modulation with death receptor-induced apoptosis. Shirwan, Haval (University of Louisville Research Foundation, Inc., USA). PCT Int. Appl. WO 2001052664 A1 20010726, 33 pp. DESIGNATED STATES: W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG, TR. (English). CODEN: PIXXD2. APPLICATION: WO 2001-US2256 20010124. PRIORITY: US 2000-PV178038 20000124; US 2000-PV215580 20000630.

AB This invention provides chimeric proteins comprising an **apoptosis -inducing mol.** fused to a member of a binding pair that is capable of binding to a selected cell that expresses a death receptor. When the selected cell is exposed in vivo or ex vivo to the chimeric protein, the selected cell undergoes apoptosis. The preferred embodiment is FasL protein fused to streptavidin. The methods of using the chimeric proteins are especially beneficial in causing activated lymphocytes to undergo apoptosis, thus modulating the immune response. Patients with conditions such as asthma or allergy, or patients undergoing transplantation with allogeneic or xenogeneic tissue are examples of patients who benefit from the methods of this invention.

L4 ANSWER 4 OF 4 MEDLINE on STN DUPLICATE 1

2000429942. PubMed ID: 10933724. Reovirus-induced apoptosis is mediated by **TRAIL.** Clarke P; Meintzer S M; Gibson S; Widmann C; Garrington T P; Johnson G L; Tyler K L. (Departments of Neurology, University of Colorado Health Sciences Center, Denver, Colorado 80262, USA.) Journal of virology, (2000 Sep) 74 (17) 8135-9. Journal code: 0113724. ISSN: 0022-538X. Pub. country: United States. Language: English.

AB Members of the tumor necrosis factor (TNF) receptor superfamily and their activating ligands transmit apoptotic signals in a variety of systems. We now show that the binding of TNF-related, apoptosis-inducing ligand (**TRAIL**) to its cellular receptors DR5 (TRAILR2) and DR4 (TRAILR1) mediates reovirus-induced apoptosis. Anti-**TRAIL** **antibody** and soluble **TRAIL** receptors block reovirus-induced apoptosis by preventing **TRAIL**-receptor binding. In addition, reovirus induces both **TRAIL** release and an increase in the expression of DR5 and DR4 in infected cells. Reovirus-induced apoptosis is also blocked following inhibition of the death receptor-associated, **apoptosis-inducing** **molecules** FADD (for FAS-associated death domain) and caspase 8.

We propose that reovirus infection promotes apoptosis via the expression of DR5 and the release of **TRAIL** from infected cells. Virus-induced regulation of the **TRAIL** apoptotic pathway defines a novel mechanism for virus-induced apoptosis.

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L5            0 L2 AND APO2L

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L6           50 L1 AND "APO-2L"

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L7           21 DUP REMOVE L6 (29 DUPLICATES REMOVED)

=> d l7 1-21 cbib abs
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L7 ANSWER 1 OF 21 MEDLINE on STN DUPLICATE 1

2004214389. PubMed ID: 15110189. TRAIL and malignant glioma. Hawkins Christine J. (Murdoch Children's Research Institute Department of Haematology and Oncology, Royal Children's Hospital Department of Paediatrics, University of Melbourne Parkville, Victoria 3052, Australia.) Vitamins and hormones, (2004) 67 427-52. Ref: 138. Journal code: 0413601. ISSN: 0083-6729. Pub. country: United States. Language: English.

AB Encouragingly, some types of cancer can now be considered treatable, with patients reasonably expecting their disease to be cured. Chemotherapy and radiation therapy are effective against these cancers because they activate the so-called intrinsic apoptosis pathways within the cancer cells. Unfortunately currently available treatments are only effective against a subset of tumor types. In contrast, other cancers, such as malignant glioma, typically do not respond to currently available therapies. Some of this resistance can be attributed to these tumor cells failing to undergo apoptosis upon anticancer treatment. Recently, considerable research attention has focused on triggering apoptosis in chemotherapy- and radiation-therapy-resistant cancer cells via an alternative route-the "extrinsic" pathway, as a means of bypassing this block in apoptosis. Binding of members of the tumor necrosis factor-alpha (TNF-alpha) family of death ligands to their receptors on the cell surface triggers this pathway. Death ligands can kill some cancer cells that are resistant to the apoptotic pathway triggered by conventional anticancer treatments. Some death ligands, such as TNF-alpha and FasL, cause unacceptable toxicity to normal cells and are therefore not suitable anticancer agents. However another death ligand, TNF-related apoptosis-inducing ligand (TRAIL)/**Apo-2L**, and **antibodies** that emulate its actions, show greater promise as candidate anticancer drugs because they have negligible effects on normal cells. This review will discuss the ability of TRAIL to induce apoptosis in malignant glioma cells and the potential clinical applications of TRAIL-based agents for glioma treatment.

L7 ANSWER 2 OF 21 MEDLINE on STN DUPLICATE 2

2004259471. PubMed ID: 15158769. Enhancement of therapeutic potential of TRAIL by cancer chemotherapy and irradiation: mechanisms and clinical implications. Shankar Sharmila; Srivastava Rakesh K. (Department of Pharmaceutical Sciences, Greenebaum Cancer Center, University of Maryland School of Pharmacy, 20 N. Pine Street, Baltimore, MD 21201, USA.) Drug resistance updates : reviews and commentaries in antimicrobial and anticancer chemotherapy, (2004 Apr) 7 (2) 139-56. Journal code: 9815369. ISSN: 1368-7646. Pub. country: Scotland: United Kingdom. Language: English.

AB Activation of cell surface death receptors by their cognate ligands triggers apoptosis. Several human death receptors (Fas, TNF-R1, TRAMP, DR4, DR5, DR6, EDA-R and NGF-R) have been identified. The most promising cytokine for anticancer therapy is TRAIL/**APO-2L**, which

induces apoptosis in cancer cells by binding to death receptors TRAIL-R1/DR4 and TRAIL-R2/DR5. The cytotoxic activity of TRAIL is relatively selective to cancer cells compared to normal cells. Signaling by TRAIL and its receptors is tightly regulated process essential for key physiological functions in a variety of organs, as well as the maintenance of immune homeostasis. Despite early promising results, recent studies have identified several TRAIL-resistant cancer cells of various origins. Based on molecular analysis of death-receptor signaling pathways several new approaches have been developed to increase the efficacy of TRAIL. Resistance of cancer cells to TRAIL appears to occur through the modulation of various molecular targets. They may include differential expression of death receptors, constitutively active Akt and NFkappaB, overexpression of cFLIP and IAPs, mutations in Bax and Bak genes, and defects in the release of mitochondrial proteins in resistant cells. Conventional chemotherapeutic and chemopreventive drugs, and irradiation can sensitize TRAIL-resistant cells to undergo apoptosis. Thus, these agents enhance the therapeutic potential of TRAIL in TRAIL-sensitive cells and sensitize TRAIL-resistant cells. TRAIL and TRAIL-receptor **antibodies** may prove to be useful for cancer therapy, either alone or in association with conventional approaches such as chemotherapy or radiation therapy. This review discusses intracellular mechanisms of TRAIL resistance and various approaches that can be taken to sensitize TRAIL-resistant cancer cells.

L7 ANSWER 3 OF 21 EMBASE COPYRIGHT 2004 ELSEVIER INC. ALL RIGHTS RESERVED. on STN DUPLICATE 3

2003286844 EMBASE Therapeutic potential of TNF-related apoptosis-inducing ligand receptor **antibodies.** Expert Opinion on Therapeutic Patents 13/7 (1081-1086) 1 Jul 2003.
Refs: 59.
ISSN: 1354-3776. CODEN: EOTPEG. Pub. Country: United Kingdom. Language: English. Summary Language: English.

AB TNF-related apoptosis-inducing ligand (TRAIL)/apoptosis-2 ligand (**Apo-2L**) is a member of the TNF superfamily and has recently been shown to induce apoptosis in transformed and cancer cells. In addition to the cytokine TRAIL, agonist **antibodies** that activate TRAIL receptors (TRAIL-R1/death receptor 4 [DR4]) and TRAIL-R2/DR5) can also induce apoptosis in receptor-bearing cells. Such **antibodies** can be used in the prevention and treatment of human diseases such as cancer, neurodegenerative, immune and inflammatory disorders and infectious disease. In this patent, Human Genome Sciences presents **antibodies** and related molecules that immunospecifically bind to TRAIL receptors (TRAIL-R1/DR4 and TRAIL-R2/DR5). The invention also relates to nucleic acid molecules encoding anti-TRAIL receptor **antibodies**, vectors and host cells containing these nucleic acids and methods for producing the same. The use of TRAIL receptor **antibody** is very promising and will likely provide useful highly targeted therapeutics in the future. Recent patent activity suggests this is an active area of therapy in the pharmaceutical industry where major attention will be paid to the design selection and formulation of a range of new **antibody**-based products.

L7 ANSWER 4 OF 21 MEDLINE on STN DUPLICATE 4

2003033470. PubMed ID: 12540490. Tumor necrosis factor-related apoptosis-inducing ligand enhances collagen production by human lung fibroblasts. Yurovsky Vladimir V. (Research Service, Veterans Affairs Maryland Health Care System and Department of Medicine, University of Maryland School of Medicine, Baltimore, Maryland 21201, USA.. vyurovsk@umaryland.edu) . American journal of respiratory cell and molecular biology, (2003 Feb) 28 (2) 225-31. Journal code: 8917225. ISSN: 1044-1549. Pub. country: United States. Language: English.

AB Tumor necrosis factor-related apoptosis-inducing ligand (TRAIL/**APO -2L**) is a member of the tumor necrosis factor family that induces apoptosis in a variety of transformed cell lines and in normal human hepatocytes and brain cells. Soluble TRAIL at high concentrations

was found to induce apoptotic death in normal human lung fibroblasts, whereas at low concentrations it was found to stimulate collagen production by these cells. Collagen alpha2(I) mRNA expression was assessed by semiquantitative reverse transcriptase/polymerase chain reaction; total soluble collagen was measured in culture supernatants by the Sircol assay. Both alpha2(I) collagen mRNA level and total soluble collagen secretion were increased upon TRAIL stimulation, with peak response (> 4-fold increase in mRNA level) at 1 ng/ml TRAIL. Analysis of the transcriptional response in TRAIL-stimulated fibroblasts, using DNA microarray hybridization, revealed an augmented expression of a number of genes involved in tissue remodeling, including those related to the transforming growth factor-beta (TGF-beta) pathway. DNA microarray results for the increase in TGF-beta1 mRNA level were confirmed by Northern blot analysis and by measurements of total active TGF-beta1 in culture supernatants. In addition, pan-specific TGF-beta **antibody** was shown to inhibit TRAIL-stimulated collagen mRNA and protein expression. These data suggest that TRAIL can enhance extracellular matrix synthesis in fibroblasts by triggering TGF-beta production that acts in an autocrine manner.

L7 ANSWER 5 OF 21 EMBASE
on STN

2003248712 EMBASE Plasmacytoid dendritic cell-derived IFN-α induces TNF-related apoptosis-inducing ligand/**Apo-2L**-mediated antitumor activity by human monocytes following CpG oligodeoxynucleotide stimulation. Kemp T.J.; Elzey B.D.; Griffith T.S.. Dr. T.S. Griffith, Department of Urology, 3204 MERF, University of Iowa, 375 Newton Road, Iowa City, IA 52242-1089, United States. thomas-griffith@uiowa.edu. Journal of Immunology 171/1 (212-218) 1 Jul 2003. Refs: 72.
ISSN: 0022-1767. CODEN: JOIMA3. Pub. Country: United States. Language: English. Summary Language: English.

AB Immunostimulatory oligodeoxynucleotides (ODN) containing the CpG motif are being tested as immune adjuvants in many disease settings. Of the human PBMC examined, plasmacytoid dendritic cells (pDC) are a major source of type I IFN upon stimulation with CpG ODN. IFNs have numerous immunostimulatory effects, including the induction of TNF-related apoptosis-inducing ligand (TRAIL)/**Apo-2L** on monocytes, NK cells, and T cells. Importantly, IFN has also been linked to antitumor responses. Thus, we tested whether CpG ODN stimulation of PBMC led to TRAIL/**Apo-2L**-induced tumor cell death. When PBMC were stimulated with CpG ODN, TRAIL/**Apo-2L**-dependent tumor cell death was observed. Further examination of CpG ODN-stimulated PBMC revealed that TRAIL/**Apo-2L** expression was limited to CD14(+) cells, which, when depleted, led to a loss of the TRAIL/**Apo-2L**-mediated tumor cell killing. Moreover, pDC depletion also abolished the TRAIL/**Apo-2L**-mediated killing of tumor cell targets. Analysis of the pDC showed IFN-α production after CpG ODN stimulation. Finally, inclusion of neutralizing IFN-α antiserum with the PBMC during CpG ODN stimulation abrogated TRAIL/**Apo-2L**-mediated tumor cell killing. These results define a mechanism by which CpG ODN induces TRAIL/**Apo-2L**-dependent killing of tumor cells by CD14(+) PBMC, in which CpG ODN-activated pDC produce IFN-α that stimulates CD14(+) PBMC to express functional TRAIL/**Apo-2L**.

L7 ANSWER 6 OF 21 MEDLINE on STN DUPLICATE 5

2003304210. PubMed ID: 12831538. Preparation and characterization of a set of monoclonal **antibodies** to TRAIL and TRAIL receptors DR4, DR5, DcR1, and DcR2. Liu Xue-Song; Zhu Yong; Han Wei-Ning; Li Ying-Na; Chen Li-Hua; Jia Wei; Song Chao-Jun; Liu Fei; Yang Kun; Li Qi; Jin Bo-Quan. (Department of Immunology, Fourth Military Medical University, Xi'an 710032, China.) Hybridoma and hybridomics, (2003 Apr) 22 (2) 121-5.
Journal code: 101131136. ISSN: 1536-8599. Pub. country: United States. Language: English.

AB The tumor necrosis factor-related apoptosis-inducing ligand (TRAIL/ **Apo 2L**) is a novel cytotoxic ligand belonging to TNF superfamily. Among TRAIL receptors, death receptor 4 (DR4) and DR5 containing death domain (DD) in their cytoplasmic region mediate apoptosis-signaling upon TRAIL binding, while decoy receptor 1 (DcR1) and DcR2 with a truncated or non-functional DD play "decoy" role. The interaction of TRAIL and TRAIL receptors plays important roles both in immunoregulation and immune pathogenesis of some diseases. In this study, we raised hybridomas secreting monoclonal **antibodies** against TRAIL (FMU1.1, 1.2, 1.3), DR4 (FMU1.4), DR5 (FMU1.5, 1.6), DcR1 (FMU1.7) and DcR2 (FMU1.8, 1.9). These MAbs could be used for fluorescent staining and flow cytometry (FCM) analysis as well as immunohistochemistry (IHC). Moreover, FMU1.1, 1.3, 1.4 and 1.5 could be used as coating **antibodies** paring corresponding polyclonal **antibodies** to develop sandwich ELISAs to quantitate the soluble TRAIL (sTRAIL), sDR4 or sDR5 in serum samples respectively. In addition, cross-linking of DR4/DR5 by FMU1.4 or FMU1.5 MAbs could induce apoptosis of some DR4/DR5-expressing tumor cells. Thus, this set of monoclonal **antibodies** against TRAIL or TRAIL receptors may be useful in expression phenotypic and functional study of TRAIL and TRAIL receptors.

L7 ANSWER 7 OF 21 CAPLUS COPYRIGHT 2004 ACS on STN

2002:107154 Document No. 136:145221 **Apo-2L** receptor agonist and CPT-11 synergism in inducing apoptosis for cancer therapy. Escandon, Enrique; Fox, Judith A.; Kelley, Sean K.; Xiang, Hong (Genentech, Inc., USA). PCT Int. Appl. WO 2002009755 A2 20020207, 84 pp. DESIGNATED STATES: W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG, TR. (English). CODEN: PIXXD2. APPLICATION: WO 2001-US23691 20010727. PRIORITY: US 2000-PV221256 20000727.

AB The invention disclosed that Apo-2 ligand or other **Apo-2L** receptor agonists and CPT-11 can act synergistically to induce apoptosis in mammalian cancer cells by up-regulating death receptor 4 or 5 gene expression. The invention provides methods for inducing apoptosis comprising exposing a mammalian cell, such as a cancer cell, to CPT-11 and one or more Apo-2 ligand receptor agonists wherein CPT-11 is administered prior to the Apo-2 ligand receptor agonist(s) to pre-treat the cells. Methods of using effective amts. of **Apo-2L** receptor agonists and CPT-11 to induce apoptosis and suppress growth of cancer cells are provided. The invention further provides various methods for the use of Apo-2 ligand receptor agonist **antibodys** (such as monoclonal **antibody** against the DR4 or DR5 receptor) and CPT-11 to induce apoptosis in mammalian cells.

L7 ANSWER 8 OF 21 SCISEARCH COPYRIGHT (c) 2004 The Thomson Corporation. on STN

2002:89476 The Genuine Article (R) Number: 514KC. Potentiation of the sensitivity of renal cell carcinoma cells to TRAIL-mediated apoptosis by subtoxic concentrations of 5-fluorouracil. Mizutani Y (Reprint); Nakanishi H; Yoshida O; Fukushima M; Bonavida B; Miki T. Kyoto Prefectural Univ Med, Dept Urol, Kyoto 6028566, Japan (Reprint); Kyoto Univ, Fac Med, Dept Urol, Kyoto 6068507, Japan; Univ Calif Los Angeles, Sch Med, Dept Microbiol Immunol & Mol Genet, Los Angeles, CA 90095 USA. EUROPEAN JOURNAL OF CANCER (JAN 2002) Vol. 38, No. 1, pp. 167-176. Publisher: PERGAMON-ELSEVIER SCIENCE LTD. THE BOULEVARD, LANGFORD LANE, KIDLINGTON, OXFORD OX5 1GB, ENGLAND. ISSN: 0959-8049. Pub. country: Japan; USA. Language: English.

ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB Cytotoxic chemotherapy has shown little antitumour activity against renal cell carcinoma (RCC). Although immunotherapy is relatively effective

against RCC, the response rate is approximately 20%. Therefore, there is an urgent need to increase this response rate. Tumour necrosis factor-related apoptosis-inducing ligand (TRAIL/**Apo-2L**) is one member of the tumour necrosis factor ligand family that selectively induces apoptosis of cancer cells. Since several cytotoxic anticancer drugs including 5-fluorouracil (5-FU) also mediate apoptosis, we reasoned that combined treatment of cancer cells with TRAIL and drugs might result in synergy and overcome the resistance of the cancer cell. This study has examined whether TRAIL can synergise with 5-FU in both cytotoxic and apoptotic assays against drug-resistant RCC cells. Cytotoxicity was determined by an 1-day microculture tetrazolium dye assay. Synergy was assessed by isobolographic analysis. Treatment of Caki-1 cells with TRAIL in combination with 5-FU resulted in a synergistic cytotoxic effect. Synergy was also achieved in freshly derived RCC cells from 3 patients. The enhanced cytotoxicity was obtained irrespective of the sequence of the treatment, but the highest cytotoxicity was observed when Caki-1 cells were treated with TRAIL and 5-FU Simultaneously. The synergy achieved in cytotoxicity with TRAIL and 5-FU was shown to be due to apoptosis. The mechanisms responsible for the synergistic cytotoxicity and apoptosis were examined. Treatment of Caki-1 cells with 5-FU enhanced the expression of p53 and bax, but had no effect on the expression of bcl-2. Incubation of Caki-1 cells with TRAIL enhanced the intracellular accumulation of 5-FU and 5-fluoro-2'-deoxyuridine 5'-monophosphate (FdUMP). Treatment of Caki-1 cells with TRAIL downregulated the expression of thymidylate synthase (TS) and dihydropyrimidine dehydrogenase (DPD) modestly, and upregulated the expression of orotate phosphoribosyltransferase (OPRT). However, the expression level of thymidine phosphorylase (TP) was not affected by TRAIL. This study demonstrates that combined treatment of RCC cells with TRAIL and 5-FU overcomes their resistance. The sensitisation obtained with freshly isolated RCC cells required low subtoxic concentrations of 5-FU. These findings support the potential application in vivo of a combination of TRAIL and 5-FU in the treatment of TRAIL/5FU-resistant RCC.

L7 ANSWER 9 OF 21 BIOSIS COPYRIGHT (c) 2004 The Thomson Corporation. on STN

2001:415132 Document No.: PREV200100415132. Method for making monoclonal **antibodies** and cross-reactive **antibodies** obtainable by the method. Ashkenazi, Avi J. [Inventor]; Chuntharapai, Anan [Inventor]; Kim, K. Jin [Inventor, Reprint author]. Los Altos, CA, USA. ASSIGNEE: Genentech, Inc.. Patent Info.: US 6252050 June 26, 2001. Official Gazette of the United States Patent and Trademark Office Patents, (June 26, 2001) Vol. 1247, No. 4. e-file.
CODEN: OGUPE7. ISSN: 0098-1133. Language: English.

AB A method of making monoclonal **antibodies** according to a mixed antigen immunization protocol is described. In addition, **antibodies** obtainable by the method are disclosed which specifically cross-react with two or more different receptors to which Apo-2 ligand (**Apo-2L**) can bind.

L7 ANSWER 10 OF 21 BIOSIS COPYRIGHT (c) 2004 The Thomson Corporation. on STN

2002:261477 Document No.: PREV200200261477. Mechanism of potentiation of Ara-C-induced apoptosis of human acute leukemia cells by **Apo-2L**/TRAIL and Smac peptide. Guo, Fei [Reprint author]; Nimmanapalli, Ramadevi [Reprint author]; Paranawithana, Shanthi [Reprint author]; Bali, Purva [Reprint author]; O'Bryan, Erica [Reprint author]; Bhalla, Kapil [Reprint author]. Moffitt Cancer Center and Research Institute, University of South Florida, Tampa, FL, USA. Blood, (November 16, 2001) Vol. 98, No. 11 Part 1, pp. 804a. print.
Meeting Info.: 43rd Annual Meeting of the American Society of Hematology, Part 1. Orlando, Florida, USA. December 07-11, 2001. American Society of Hematology.
CODEN: BLOOAW. ISSN: 0006-4971. Language: English.

AB Previous studies from our laboratory have shown that treatment with high dose Ara-C (HIDAC: 10 or 100 muM for 4 to 6 hours) increases the protein expression of the death receptor DR5, but not of **Apo-2L** /TRAIL or the non-signaling decoy receptors DcR1 and 2. Consequently, pre-treatment with and Ara-C enhanced **Apo-2L** /TRAIL-induced apoptosis of the human AML HL-60 and Jurkat T cells (Blood, 96:3900, 2000). Utilizing RiboQuant Multi-Probe RNase Protection Assay, we have now determined that Ara-C mediated upregulation of DR5 is post-transcriptional, since it is not preceded by an increase in the mRNA levels of DR5, or of DR4 and **Apo-2L**/TRAIL. Jurkat cells were sequentially exposed to 10 muM Ara-C for 4 hours followed by **Apo-2L**/TRAIL (100 ng/ml), and cell lysates were subjected to immunoprecipitation with anti-DR5 **antibody** followed by immunoblotting with anti-FADD and caspase-8 **antibodies** to determine the assembly of **Apo-2L**/TRAIL-induced DISC and its caspase-8-cleavage activity. Pre-treatment with Ara-C significantly increased **Apo-2L**/TRAIL-induced DISC assembly and activity resulting in Bid processing and cytosolic accumulation of cytochrome (cyt) c and Smac (second mitochondria-derived activator of caspases). This was associated with increased processing of procaspase-9 and -3, downregulation of XIAP and survivin and PARP cleavage activity of caspase-3. Transient transfection of the pcDNA plasmid containing full-length smac cDNA with a FLAG tag at the C terminus resulted in overexpression of Smac in Jurkat cells (Jurkat/Smac) without the induction of caspase-3 activity and apoptosis. However, treatment with Ara-C or **Apo-2L**/TRAIL for 24 hours induced significantly more apoptosis of Jurkat/Smac versus the control Jurkat/Zeo cells ($p<0.05$). This was associated with a significantly greater cytosolic accumulation of Smac as well as increased processing of caspase-3, XIAP and PARP. Importantly, co-treatment with the N-terminus 7 AA (AVPIAQK, Smac-7) or 4 AA peptide (AVPI, Smac-4, which is homologous to the N-terminus of Drosophila proteins Hid, Grim and Reaper) also significantly enhanced Ara-C or **Apo-2L**/TRAIL-induced apoptosis of Jurkat cells. Treatment with Smac-7 or Smack-4 alone was not cytotoxic. These findings demonstrate that combined treatment with **Apo-2L**/TRAIL and/or Smac peptide with Ara-C may increase its antitumor cytotoxic effects by potentiating the extrinsic and intrinsic pathway for apoptotic signaling and the effector caspase activity triggered by Ara-C. These results also suggest that a combined treatment with HIDAC followed by **Apo-2L**/TRAIL plus Smac4 or Smac7 may be a highly effective combination against acute leukemias.

L7 ANSWER 11 OF 21 CAPLUS COPYRIGHT 2004 ACS on STN
2000:881199 Document No. 134:28448 Apoptosis of tumor cells by **Apo -2L** receptor agonist and camptothecin combination therapy. Ashkenazi, Avi J.; Benyunes, Mark C.; Schwall, Ralph H. (Genentech, Inc., USA). PCT Int. Appl. WO 2000075191 A2 20001214, 51 pp. DESIGNATED STATES: W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG. (English). CODEN: PIXXD2. APPLICATION: WO 2000-US15512 20000607. PRIORITY: US 1999-PV138240 19990609.

AB The authors disclose the use of TRAIL, **Apo-2L** receptor agonists, and camptothecin 11 (CPT-11) to synergistically induce apoptosis and suppress growth of cancer cells. In one example, growth of colon carcinoma cells in inoculated mice was suppressed by either Apo-2 ligand or CPT-11, however, growth resumed after several days. Mice treated with a combination of Apo-2 ligand and CPT-11 exhibited tumor shrinkage and elimination in a majority of the animals. In a second example, a monoclonal **antibody** against DR4 receptor caused significant

delay in tumor progression. The combination of DR4 **antibody** and CPT-11 delayed tumor progression to a greater extent than either agent alone.

L7 ANSWER 12 OF 21 MEDLINE on STN DUPLICATE 6
2001061025. PubMed ID: 11114725. Bcl-XL protects pancreatic adenocarcinoma cells against CD95- and TRAIL-receptor-mediated apoptosis. Hinz S; Trauzold A; Boenicke L; Sandberg C; Beckmann S; Bayer E; Walczak H; Kalthoff H; Ungefroren H. (Research Unit Molecular Oncology, Clinic for General Surgery and Thoracic Surgery, Christian-Albrechts-University, Kiel, Germany.) Oncogene, (2000 Nov 16) 19 (48) 5477-86. Journal code: 8711562. ISSN: 0950-9232. Pub. country: England: United Kingdom. Language: English.

AB In this study we sought to clarify the role of the proapoptotic potential of mitochondria in the death pathway emanating from the TRAIL (**APO -2L**) and CD95 receptors in pancreatic carcinoma cells. We focused on the role of the Bcl-2 family member Bcl-XL, using three pancreatic carcinoma cell lines as a model system, two of which have high (Panc-1, PancTuI) and one has low (Colo357) Bcl-XL expression. In these cell lines, the expression of Bcl-XL correlated with sensitivity to apoptosis induced by TRAIL or anti-CD95. Flow cytometric analysis revealed cell surface expression of TRAIL-R1 and TRAIL-R2 on PancTuI and Colo357, and TRAIL-R2 on Panc-1 cells. In Colo357 cells retrovirally transduced with Bcl-XL, caspase-8 activation in response to treatment with TRAIL or anti-CD95 **antibody** was not different from parental cells and EGFP-transfected controls, however, apoptosis was completely suppressed as measured by the mitochondrial transmembrane potential deltapsim, caspase-3 activity (PARP cleavage) and DNA-fragmentation. Inhibition of Bcl-XL function by overexpression of Bax or administration of antisense oligonucleotides against Bcl-XL mRNA resulted in sensitization of Panc-1 cells to TRAIL and PancTuI cells to anti-CD95 **antibody**-induced cell death. The results show that Bcl-XL can protect pancreatic cancer cells from CD95- and TRAIL-mediated apoptosis. Thus, in these epithelial tumour cells the mitochondrially mediated 'type II' pathway of apoptosis induction is not only operative regarding the CD95 system but also regarding the TRAIL system.

L7 ANSWER 13 OF 21 MEDLINE on STN DUPLICATE 7
2000283278. PubMed ID: 10825131. Radiation and the Apo2L/TRAIL apoptotic pathway preferentially inhibit the colonization of premalignant human breast cells overexpressing cyclin D1. Zhou Q; Fukushima P; DeGraff W; Mitchell J B; Stetler Stevenson M; Ashkenazi A; Steeg P S. (Women's Cancers Section, Division of Clinical Sciences, National Cancer Institute, Bethesda, Maryland 20892, USA.) Cancer research, (2000 May 15) 60 (10) 2611-5. Journal code: 2984705R. ISSN: 0008-5472. Pub. country: United States. Language: English.

AB The role of cyclin D1 overexpression in human breast premalignancy was investigated using immortal, nontumorigenic MCF-10A cells. Previous work documented that cyclin D1 overexpression promoted in vitro anchorage-independent colonization. We now report that the colonization of MCF-10A cyclin D1 transfectants was preferentially inhibited by gamma-radiation and specific classes of apoptosis inducers [Apo-2 ligand (**Apo-2L**), but not tumor necrosis factor alpha].
Antibody inhibition studies and semiquantitative PCR indicated that radiation inhibition of colonization was partially mediated via the Apo2L/TRAIL pathway. The apoptotic removal of cyclin D1-overexpressing, colonization-competent premalignant breast cells by Apo2L/TRAIL or other biologicals may represent a novel approach to the prevention of breast cancer.

L7 ANSWER 14 OF 21 EMBASE COPYRIGHT 2004 ELSEVIER INC. ALL RIGHTS RESERVED. on STN
2000419468 EMBASE Sensitivity to TRAIL/**APO-2L**-mediated apoptosis in human renal cell carcinomas and its enhancement by topotecan. Dejosez M.; Ramp U.; Mahotka C.; Krieg A.; Walczak H.; Gabbert H.E.;

Gerharz C.D.. C.D. Gerharz, Institute of Pathology, Heinrich Heine University, PO Box 101 007, D-40225 Duesseldorf, Germany. Cell Death and Differentiation 7/11 (1127-1136) 2000.
Refs: 56.
ISSN: 1350-9047. CODEN: CDDIEK. Pub. Country: United Kingdom. Language: English. Summary Language: English.

AB TRAIL(**APO-2L**) is a newly identified member of the TNF family and induces apoptosis in cancer cells without affecting most non-neoplastic cells, both in vitro and in vivo. Our study focused on the expression and function of TRAIL and its receptors in renal cell carcinoma (RCC) cell lines of all major histological types. Here, we demonstrate that all RCC cell lines express TRAIL as well as the death-inducing receptors TRAIL-R1 (DR4) and TRAIL-R2 (Killer/DR5). Exposure to TRAIL induced apoptosis in 10 of 16 RCC cell lines. Remarkably, five of six TRAIL-resistant RCC cell lines exhibited high levels of TRAIL expression. Topotecan, a novel topoisomerase I inhibitor, induced upregulation of TRAIL-R2 as well as downregulation of TRAIL. Neutralization of TRAIL with recombinant soluble TRAIL-R1-Fc and TRAIL-R2-Fc failed to inhibit topotecan-induced apoptosis indicating that topotecan-induced cell death can occur in a TRAIL- independent fashion. However, exposure to topotecan resulted in an enhancement of TRAIL-induced apoptosis in all primarily TRAIL-resistant RCC cell lines. This synergistic effect of cotreatment with Topotecan and TRAIL may provide the basis for a new therapeutic approach to induce apoptosis in otherwise unresponsive RCC.

L7 ANSWER 15 OF 21 SCISEARCH COPYRIGHT (c) 2004 The Thomson Corporation. on STN

2000:299648 The Genuine Article (R) Number: 304HB. The CD95 (APO-1/Fas) and the TRAIL (**APO-2L**) apoptosis systems. Walczak H; Krammer P H (Reprint). GERMAN CANC RES CTR, TUMORIMMUNOL PROGRAM, D-69120 HEIDELBERG, GERMANY (Reprint); GERMAN CANC RES CTR, TUMORIMMUNOL PROGRAM, D-69120 HEIDELBERG, GERMANY. EXPERIMENTAL CELL RESEARCH (10 APR 2000) Vol. 256, No. 1, pp. 58-66. Publisher: ACADEMIC PRESS INC. 525 B ST, STE 1900, SAN DIEGO, CA 92101-4495. ISSN: 0014-4827. Pub. country: GERMANY. Language: English.

L7 ANSWER 16 OF 21 CAPLUS COPYRIGHT 2004 ACS on STN

1999:795853 Document No. 132:34769 Method for making monoclonal **antibodies** and cross-reactive **antibodies** obtainable by the method. Ashkenazi, Avi J.; Chuntharapai, Anan; Kim, K. Jin (Genentech, Inc., USA). PCT Int. Appl. WO 9964461 A2 19991216, 58 pp. DESIGNATED STATES: W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG. (English). CODEN: PIXXD2. APPLICATION: WO 1999-US13197 19990610. PRIORITY: US 1998-96637 19980612.

AB A method of making monoclonal **antibodies** according to a mixed antigen immunization protocol is described. In addition, **antibodies** obtainable by the method are disclosed which specifically cross-react with two or more different receptors to which Apo-2 ligand (**Apo-2L**) can bind. Thus, immunogens comprising receptor immunoadhesins, i.e. DR4-IgG, Apo-2-IgG, DcR1-IgG, and DcR2-IgG, were prepared as immunogens for raising monoclonal **antibodies.** These **antibodies** are useful for inducing apoptosis of mammalian cancer cells.

L7 ANSWER 17 OF 21 CAPLUS COPYRIGHT 2004 ACS on STN

1999:166717 Document No. 130:222132 Recombinant expression, sequence, and biol. and therapeutics uses of human RTD, a receptor for Apo-2 ligand/TRAIL. Ashkenazi, Avi J.; Gurney, Austin (Genentech, Inc., USA). PCT Int. Appl. WO 9910484 A1 19990304, 58 pp. DESIGNATED STATES: W: AL,

AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, GM, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG. (English). CODEN: PIXXD2. APPLICATION: WO 1998-US14552 19980714. PRIORITY: US 1997-918874 19970826.

AB The invention relates to the identification, isolation, and recombinant production of novel human polypeptides designated RTD and to anti-RTD **antibodies.** Two human cDNA clones are provided encoding the RTD polypeptides, which are thought to be members of the tumor necrosis factor receptor (TNFR) family. The RTD polypeptides are shown to bind Apo-2 ligand (also referred to as TRAIL) and block **Apo-2L** apoptosis, supporting the belief that RTD is a receptor for Apo-2 ligand. The invention also provides chimeric mols. comprising RTD polypeptides fused to an Ig mol. or to a heterologous polypeptide. Further, the invention provides a vector comprising the RTD nucleic acid mols., a host cell comprising the vector and methods for recombinant production The cDNA and amino acid sequences of the two isoforms of human RTD receptor are provided. The two human RTD receptor isoforms were found to be identical, except for one amino acid located at codon 310. The human RTD receptor gene was found to be expressed in fetal kidney, liver and lung, and in multiple adult tissues, particularly in testis and kidney. Like DR5, DcR1 and DR4 genes, the human RTD receptor gene was mapped to chromosome 8q21.

L7 ANSWER 18 OF 21 MEDLINE on STN

1999410746. PubMed ID: 10479402. Regulation of APO-2 ligand/trail expression in NK cells-involvement in NK cell-mediated cytotoxicity. Johnsen A C; Haux J; Steinkjer B; Nonstad U; Egeberg K; Sundan A; Ashkenazi A; Espevik T. (Department of Cancer Research and Molecular Biology, Norwegian University of Science and Technology, Trondheim, Norway.. Ann-Charlotte.Johnsen@medisin.ntnu.no) . Cytokine, (1999 Sep) 11 (9) 664-72. Journal code: 9005353. ISSN: 1043-4666. Pub. country: United States. Language: English.

AB **Apo-2L** is a new member of the tumour necrosis factor (TNF) family shown to induce apoptosis in a number of tumour cell lines. **Apo-2L** mRNA is expressed by numerous human tissues. Here we report that **Apo-2L** is expressed and utilized by human Natural Killer (NK) cells. NK cells were shown to express surface **Apo-2L** in response to interleukin 2 (IL-2) activation, and this response was restricted to the CD3(-)population of the NK cells. **Apo-2L** mRNA and intracellular **Apo-2L** were present in both CD3(-)and CD3(+)NK cells; however, increased expression in response to IL-2 was only observed in CD3(-)CD56(+)cells. Also, IL-2-activated NK cells were shown to utilize membrane-bound **Apo-2L** in mediating lysis of Jurkat cells. Furthermore, **Apo-2L**-induced apoptosis of Jurkat cells was more rapid than FasL-induced apoptosis, indicating an important and distinct role for **Apo-2L** in apoptotic cell destruction. In conclusion, we report that NK cells express **Apo-2L** and that IL-2 activated CD3(-)NK cells utilize the **Apo-2L** pathway in mediating target cell lysis. Copyright 1999 Academic Press.

L7 ANSWER 19 OF 21 CAPLUS COPYRIGHT 2004 ACS on STN

1998:761975 Document No. 130:21371 Cloning and cDNA sequence of human Apo-2 receptor and its use in modulating apoptosis. Ashkenazi, Avi J.; Adams, Camellia W.; Chuntharapai, Anan; Kim, Kyung Jin (Genentech, Inc., USA). PCT Int. Appl. WO 9851793 A1 19981119, 134 pp. DESIGNATED STATES: W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, GM, GW, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE,

DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG. (English). CODEN: PIXXD2. APPLICATION: WO 1998-US9704 19980514. PRIORITY: US 1997-857216 19970515.

AB Novel human cDNA clones encoding polypeptides, designated Apo-2, which are capable of modulating apoptosis are provided. Apo-2 is a member of the tumor necrosis factor receptor family; full-length native sequence human Apo-2 polypeptide exhibits some similarities to some known TNFRs, including a cytoplasmic death domain region and extracellular cysteine-rich repeats. Apo-2 polypeptide is capable of triggering caspase-dependent apoptosis and activating NF-κB. A soluble extracellular domain of Apo-2 binds Apo-2 ligand (**Apo-2L**) and can inhibit Apo-2 ligand function. The Apo-2 gene is localized to human chromosome 8p21. Compns. including Apo-2 chimeras, nucleic acid encoding Apo-2, and **antibodies** to Apo-2 are also provided.

L7 ANSWER 20 OF 21 MEDLINE on STN DUPLICATE 8

96278649. PubMed ID: 8663110. Induction of apoptosis by Apo-2 ligand, a new member of the tumor necrosis factor cytokine family. Pitti R M; Marsters S A; Ruppert S; Donahue C J; Moore A; Ashkenazi A. (Department of Molecular Oncology, Genentech, Inc., South San Francisco, California 94080-4990, USA.) Journal of biological chemistry, (1996 May 31) 271 (22) 12687-90. Journal code: 2985121R. ISSN: 0021-9258. Pub. country: United States. Language: English.

AB Cytokines in the tumor necrosis factor (TNF) family regulate development and function of the immune system. We have isolated a new member of this family, designated Apo-2 ligand (**Apo-2L**), via an expressed sequence tag. **Apo-2L** is a 281-amino acid protein, related most closely to Fas/Apo-1 ligand. Transfected **Apo-2L** is expressed at the cell surface with its C terminus exposed, indicating a type II transmembrane protein topology. Like Fas/Apo-1 ligand and TNF, the C-terminal extracellular region of **Apo-2L** (amino acids 114-281) exhibits a homotrimeric subunit structure. Soluble **Apo-2L** induces extensive apoptosis in lymphoid as well as non-lymphoid tumor cell lines. The effect of **Apo-2L** is not inhibited by soluble Fas/Apo-1 and TNF receptors; moreover, expression of human Fas/Apo-1 in mouse fibroblasts, which confers sensitivity to induction of apoptosis by agonistic anti-Fas/Apo-1 **antibody**, does not confer sensitivity to **Apo-2L.** Hence, **Apo-2L** acts via a receptor which is distinct from Fas/Apo-1 and TNF receptors. These results suggest that, along with other family members such as Fas/Apo-1 ligand and TNF, **Apo-2L** may serve as an extracellular signal that triggers programmed cell death.

L7 ANSWER 21 OF 21 MEDLINE on STN DUPLICATE 9

96385443. PubMed ID: 8793301. Activation of apoptosis by Apo-2 ligand is independent of FADD but blocked by CrmA. Marsters S A; Pitti R M; Donahue C J; Ruppert S; Bauer K D; Ashkenazi A. (Department of Molecular Oncology, Genantech Inc., South San Francisco, California 94080, USA.) Current biology : CB, (1996 Jun 1) 6 (6) 750-2. Journal code: 9107782. ISSN: 0960-9822. Pub. country: ENGLAND: United Kingdom. Language: English.

AB A new member of the tumor necrosis factor (TNF) cytokine family, designated Apo-2 ligand (Apo-21) [1] or TRAIL [2], has been shown recently to induce apoptosis in various tumor cell lines; however, its biological role is unknown. Here, we show that Apo-21, activated apoptosis in T-cell-enriched cultures of peripheral blood lymphocytes stimulated by interleukin-2 (IL-2), but not in unstimulated cells. This finding suggests that, like Fas/Apo-1 ligand and TNF [3-5], **Apo-2L** may play a role in regulating post-stimulation apoptosis of mature lymphocytes. Studies on the mechanism of **Apo-2L** action demonstrated marked membrane blebbing, a hallmark of apoptosis, within a few minutes of the addition of **Apo-2L** to tumor cells. Ectopic expression of a dominant negative mutant of FADD, a cytoplasmic protein that mediates death signalling by Fas/Apo-1 and by TNF receptor type 1 (TNFR1) [6-9], inhibited the induction of apoptosis by

anti-Fas/Apo-1 **antibody**, but had little effect on **Apo-2L** function. In contrast, expression of CrmA, a cowpox virus-derived inhibitor of the Ced-2-like proteases ICE [10] and CPP32/Yama [11,12], blocked the induction of apoptosis by either **Apo-2L** or anti-Fas/Apo-1 **antibody.** These results suggest that **Apo-2L** activates a rapid, FADD-independent pathway to trigger a cell-death programme that requires the function of cysteine proteases such as ICE or CPP32/Yama.

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=> s ruben s?/au
L8         1457 RUBEN S?/AU

=> s l8 and "AIM-I" antibody
L9            0 L8 AND "AIM-I" ANTIBODY

=> s l8 and "AIM-I"
L10           1 L8 AND "AIM-I"

=> d l10 cbib abs

L10  ANSWER 1 OF 1  CAPLUS  COPYRIGHT 2004 ACS on STN
1997:623179  Document No. 127:315580  Apoptosis-inducing molecule I and its
     encoding cDNA from human tissues.  Ruben, Steven M. (Human
     Genome Sciences, Inc., USA; Ruben, Steven M.).  PCT Int. Appl. WO 9733899
     A1 19970918, 83 pp.  DESIGNATED STATES: W:  AM, AU, BG, BR, BY, CA, CN,
     CZ, EE, FI, GE, HU, JP, KG, KP, KR, KZ, LT, LV, MD, MN, MX, NO, NZ, PL,
     RO, RU, SG, SI, SK, TJ, TM, UA, US, UZ, VN; RW: AT, BE, CH, DE, DK, ES,
     FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE.  (English).  CODEN: PIXXD2.
     APPLICATION: WO 1996-US3773 19960314.
AB   The invention relates to apoptosis-inducing mol. I (AIM-
     I) polypeptides, polynucleotides encoding the polypeptides,
     methods for producing the polypeptides, in particular by expressing the
     polynucleotides, and agonists and antagonists of the polypeptides.
     AIM-I cDNA was discovered in a cDNA library derived from
     cells of a human pancreatic tumor and shown to contain an open reading
     frame encoding 281 amino acid residues with 48.6% similarity and 22.9%
     identity to human Fas ligand.  Northern blot anal. shows that AIM
     -I mRNA is abundant in human heart, bone marrow, CD4+ and CD19+
     peripheral blood lymphocytes, and less so in lung and kidney tissue.
     Cloning of human AIM-I cDNA was demonstrated by
     expression in Escherichia coli using the bacterial expression vector pQE9,
     expression in a baculovirus expression system using the pA2 vector,
     expression in COS cells using the pcDNAI/Amp vector, and gene therapeutic
     expression.  The invention further relates to methods for utilizing such
     polynucleotides, polypeptides, agonists and antagonists for applications,
     which relate, in part, to research, diagnostic and clin. arts.

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